REMARKS

In this non-final Official Action, the Examiners have unilaterally and without applicants' consent imposed an election of species in addition to Applicants' provisional election with traverse of claims 11-14 constituting Group III; and have unilaterally and without applicants' consent withdrawn dependent claims 13 and 14 respectively as being drawn to a non-elected invention. In addition, the Examiners have provisionally rejected claims 11 and 12 under the judicially created doctrine of double patenting over claims 11 and 12 of copending U.S. Patent Application Serial No. 09/276,868. Finally, the Examiners have rejected claims 11 and 12 respectively under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,654,273 of Gallo *et al.*.

In response, applicants have amended the language of independent claim 11; enclose herewith a Terminal Disclaimer in compliance with 37 C.F.R. 1.321; and address each issue now in controversy directly and forthrightly. By the claim amendment, the enclosed Terminal Disclaimer document, and the discussion presented hereinafter, applicants believe they have overcome and obviated each basis for rejection stated by the Examiners in the instant non-final Official Action.

It is applicants' express purpose and desire to advance the prosecution of the present application substantively and meaningfully in the most

expeditious manner possible. However, effective patent prosecution requires that applicants' undersigned attorney not merely respond to the Examiners' stated bases for rejection, but rather present and advocate different and often contrary views, positions, facts, and points of law which frequently stand in opposition to and often are in conflict with the Examiners' stance. It is therefore hoped and believed that all of the remarks and statements presented hereinafter will be recognized as proper and objective attempts to persuade the Examiners to consider a different point of view and accept an alternative conclusion; and that none of the comments, explanations and/or criticisms presented hereinafter are directed at the Examiners' status, personality, or professionalism. On this basis therefore, applicants and their undersigned attorney will address each of the issues now in controversy.

I. The Examiners' Imposed Election Of Species:

A. The Examiners of record have unilaterally and without applicants' consent imposed an election of species; and, for reasons known only to the Examiners, chosen to misinterpret and wrongly presume that applicants' identification of SEQ ID NO:12 as one representative embodiment of the PR-39 derived oligopeptide family (defined by amended independent claim 11) constitutes an election of species for that sequence alone for prosecution on the merits [Page 2, 4th paragraph, of the instant Official Action]. The

Examiners' actions in this regard are erroneously based and completely unjustified.

Applicants also respectfully submit that the Examiners present actions and decisions are directly opposite to and contradict the Examiners' explicit statements and formal positions presented at page 4, 2nd paragraph of the Office Communication mailed April 7, 2003 which demanded a Restriction Requirement, but without asking for any election of species. Applicants' formal Response mailed April 15th, 2003 not only traversed the Restricted Requirement in its entirety, but also explicitly stated that Applicants did not then and do not now make any election of species whatsoever [Page 2, 2nd paragraph of the Reply mailed April 15, 2003].

The Examiners have clearly misread and misinterpreted applicants' remarks and positions; and decidedly ignored and evaded from their stated formal stance and legally estopped views and position - which nevertheless are factually and legally binding upon the Examiners as the "law of the case" under the legal doctrine of estoppel and the legal constraints imposed by the prosecution file history to date.

Moreover, it appears that the Examiners believe that their prior stated stance and legal position [in the Office Communication mailed April 7th, 2003] can be altered and changed unilaterally at any time and at the Examiners' whim and pleasure; and that applicants' belief, trust and reliance

that the Examiners are factually obligated and legally bound to maintain consistency of legal position - as well as their duty to meet and keep their word and commitments as stated - is merely an irrelevant obstacle and outdated concept which can be ignored and forgotten whenever and however it suits the Examiners' convenience.

Applicants respectfully submit and maintain that the Examiners have exceeded their lawful authority; have acted unilaterally and without applicants' consent to wrongfully impose an election of species; and have caused substantive harm and prejudicial error to applicants by wrongfully limiting and confining the prosecution of the present application to only claims 11 and 12.

B. The Examiners have also taken an unfortunate view and indefensible position concerning the legal force and lawful effect of sequence identification numbers such as SEQ ID NO:12. The Examiners' stance is explicitly stated at Page 2, last sentence of the instant Official Action in the following words.

> "While applicant's arguments regarding the previous prosecution history are noted, the examiner is not bound by that history, as there were previously no available listing for searching (paper #9, 12/20/00)."

The Examiners' stated view and position is factually erroneous and legally insupportable. The Examiners are factually controlled and legally bound by their stated views and positions in the Official Communications as well as by the prosecution file history of the present invention as a whole, as are applicants.

Moreover, the present procedure for providing sequence identity listings or numbers for amino acid residues and peptides are solely engrafted paper form and processing requirements which are legally based and grounded upon the 35 U.S.C. 112, 1st paragraph statutory requirement; and these SEQ ID NO. details are solely intended to augment the adequacy of description and enablement requirements for the invention as claimed. The sequence identification listings have no other bearing or legal relevance as such. Accordingly, the Examiners cannot use them as an excuse to act arbitrarily, subjectively or unilaterally; or to avoid taking responsibility for the prosecution file history to date..

In addition, the Examiners cannot presume to base their wrongful views and position on the alleged authority of the Manuel Of Patent Examining Procedure (M.P.E.P.). The attention of the Examiners is directed to the "Foreword" page, an introductory text which has appeared in similar language in every edition and revision of the M.P.E.P.; and states in pertinent part

..."The Manuel does not have the force of law or the force of the Patent Rules in Title 37, Code of Federal Regulations....Examiners will be governed by the applicable statues, the Rules of Practice, decisions, and orders and instructions issued by the Commissioner and the Assistant Commissioners..."

Thus the M.P.E.P. itself is merely an informal guide; constitutes only an advisory manual for the Examiners; and is a handbook of procedures which merely summarizes the various legal rights, lawful requirements, and legal duties and obligations mandated by Title 35, by Title 37 of the Code of Federal Regulations, and by the controlling caselaw decisions.

Accordingly, the existence or non-existence of sequence identification listings as such are purely paper and process formalities; and have nothing whatsoever to do with the legal constraints, duties and obligations existing upon the Examiners via the legal doctrine of estoppel and the legal authority and force of the prosecution file history of the case - as the recent caselaw decisions on this subject clearly demonstrate and prove. Equally important, the obligations imposed on the Examiners by the legal doctrine of estoppel - and the duty and constraints imposed by the legal concept of prosecution file history estoppel in particular - deny, refute and show the impossibility of the Examiners' view and position as stated in the instant Official Action.

C. Applicants and their undersigned attorney are disappointed that the Examiners have chosen to splinter the membership of a unitary PR-39

derived oligopeptide family into minor differences of peptide size which range from 15 to 8 amino acid residues in length. Applicants believe that such final restriction and unilateral election of species is a prejudicial error of both judgement and discretion: It represents an unfortunate failure by the Examiners to consider the direct relationship and characteristics shared by a single and well defined family member ship of peptides; is a decision to ignore the essential elements and requirements commonly shared among by each of claims 11-14 respectively; and is a choice to ignore the integrated nature of the PR-39 derived oligopeptide family and subject matter as a whole which is applicants' invention.

Applicants also respectfully submit that the Examiners' excuse and reliance upon the minor differences existing between SEQ ID NOS: 12, 13 and 14 individually is an artifice which defies logic. However, by taking this factual stance and legal position, applicants' undersigned attorney respectfully points out that the Examiners are engaging in a subtle form of self-deception; and have unfortunately chosen flawed, subjective, and insupportable grounds upon which to base their decision.

For all these reasons, applicants and their unsigned attorney now respectfully request the Examiners to reconsider their decision; to withdraw the unilaterally imposed election of species in its entirely; to rejoin claims 13

and 14 to claims 11 and 12 in the present application; and to consider claims 11-14 together and collectively as a single, unitary invention.

II. The Double Patenting Rejection

The Examiners have provisionally rejected pending claims 11 and 12 under the judicially created doctrine of double patenting; and rejected claims 11 and 12 in the present application over claims 11 and 12 of copending USSN 09/276,868. The rejection, however, is a provisional double patent rejection since the allegedly conflicting claims in USSN 09/276,868 have not yet been allowed or included in an issued patent.

In response, applicants enclose herewith a Terminal Disclaimer whose text is fully in compliance with the requirements of 37 C.F.R. 1.32©); and constitutes a legal commitment which permanently joins and forever links the two copending patent applications together for the duration of their legal lives. Moreover, by the submission of the enclosed Terminal Disclaimer document, applicants have properly and completely legally overcome the instant provisional double patenting rejection basis as well as obviated and removed the underlying basis for rejection in its entirety.

For all these reasons, applicants therefore respectfully request that the Examiners reconsider their stated position and withdraw this ground of rejection against the presently pending claims.

III. The Rejection Based On 35 U.S.C. 102 (b)

The Examiners have rejected claims 11 and 12 under 35 U.S.C. 102(b) as anticipated by the Gallo et al. reference [U.S. Patent No. 5,654,273]. The Examiners state that: (a) This cited and applied patent reference discloses a method for treating angiogenesis using PR-39 compositions; (b) that merely because SEQ ID NO:1 in the reference is identical to SEQ ID NO:3 of the present application, that this fact is a sound reason for a rejection on this basis; and ©) that because the Examiners believe that native PR-39 would inherently possess the property of causing an alteration in proteasome-mediated degradation of peptides, that this also is a proper reason for a rejection based on anticipation.

In reply, applicants respectfully maintain that the Examiners have not presented any facts or established any evidence with the requisite degree of substantial certainty which proves any prior art composition as having properties for angiogenesis stimulation similar to capabilities of the short-length oligopeptide compositions recited by amended claims 11 and 12 (or the oligopeptide compositions defined by withdrawn claims 13 and 14). Moreover, the Examiners' given basis for rejection as stated fails to meet minimal legal requirements and may not be properly employed as a legal basis for rejection. This is demonstrated factually by the absence of relevant supporting information, knowledge, or data within the single cited and applied reference, the Gallo *et al.* '273 patent, as is demonstrated hereinafter.

Under these circumstances, therefore, a summary review of the requisite legal standards concerning anticipation under Section 102(b) is properly in order.

A. The Correct Legal Standards For Determining Novelty

It is a legal axiom and a first principle that the language of the claim defines the scope of the invention [Yale Lock Mfg. Co. V. Greenleaf, 117 U.S. 554 at 559 (U.S. Sup. Ct. 1886)]. Moreover, while the claim may be illustrated by the disclosure and description of the Specification text, the nature and definition of applicants' invention is focused upon and limited to only the wording actually recited by the claim. Thus, no person can either broaden or narrow the claim wording to introduce or yield something different than what the language of the claim sets forth itself [Continental Paper Bag Co. V. Eastern Paper Bag Co., 210 U.S. 405 at 419 (U.S. Sup Ct. 1908); Cimiotti Unhairing Co. v. American Fur Ref. Co., 198 U.S. 399 at 410 (U.S. Sup. Ct. 1905)]. In particular, the actual wording of a claim cannot be engrafted upon or enlarged by unilateral insertion of any concept, text, or detail contained within the Specification text [Autogiro Co. Of Am. v. United States, 155 U.S.P.Q. 697 at 701 (Ct. Cl. 1967)].

Also, as a matter of long established law, anticipation under 35 U.S.C. 102(b) requires exact identity of the claimed composition (or process) within a conventionally known substance or procedure existing previously in the

prior art. The claimed composition (or the claimed process), including each element and recited characteristic of the recited composition, must be described or embodied, directly or indirectly, within a single reference. Anticipation thus requires exact identity or effective duplication of applicant's invention as actually claimed; and the single reference of record must describe applicant's claimed invention sufficiently and in detail such that a person of ordinary skill in that field has possession of the invention itself. Also, in deciding the issue of anticipation, the Examiner must identify each requisite element recited within the wording of the claims; determine their meaning in light of the Specification; and identify the existence and presence for each of the corresponding elements as being disclosed in the allegedly anticipating reference [Scripts Clinical and Research Foundation vs. Genentech Inc., 18 U.S.P.Q. 2d 1001 (Fed. Cir. 1991); Glaverbel Society Anonyme vs. Northlake Marketing and Supply Inc., 35 U.S.P.Q. 2d 1496 (Fed. Cir. 1995)].

It is useful here also to identify the legal basis and standard for obviousness under 35 U.S.C. 103. Where applicant's claimed subject matter can be rejected as obvious in view of a single reference or a combination of prior art references, a proper analysis must consider inter alia two factors: (1) whether the cited and applied prior art of record would have suggested to those of ordinary skill in the art that they should carry out the claimed process or make the claimed composition; and (2) whether the cited and

applied prior art would also have revealed that in so carrying out or making, those of ordinary skill would have a reasonable expectation of success [In re Dow Chemical Company, 5 U.S.P.Q. 2d 1529 (Fed. Cir. 1988)]. Both the suggestion and the reasonable expectation of success must be found within the prior art references(s) themselves and not in applicant's disclosure [In re Vaeck, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991)]. In addition, the same inquiry must be carried out in the context of a purported "obvious modification" of the prior art information. The mere fact that the prior art might be modified in the manner suggested by an Examiner does not make that modification obvious unless the prior art suggested the desirability of the modification [In re Fritch, 23 U.S.P.Q. 2d 1780 (Fed. Cir. 1992) and the references cited therein].

Applicants therefore respectively affirm and submit that the Examiners' stated views and conclusions in the instant Official Action have failed to conform to the legal standard and requirements necessary for a rejection based upon anticipation (as well as for obviousness). A detailed review of the substantive factual content within the single cited and applied patent reference will reveal the multiple errors in the Examiners' stated views and position.

B. The Content of the Cited And Applied References of Record

Applicants and their undersigned attorney will now review the single cited and applied prior art reference in detail, the Gallo *et al.* patent, No. 5,654,273.

In conducting this review of the facts disclosed within this cited and applied prior art reference, applicants will take special care to point out what the goals and objectives for the referenced invention are, as explicitly stated within the reference; the means and manner in which the referenced invention is said to be functional and operative; and, the explicitly recognized limitations and restrictions of the referenced invention as stated by the patent itself. The Examiners' attention is directed particularly to these points of information as the best evidence and proof of the Examiners' repeated errors.

1. The Gallo *et al.* '273 patent and invention is explicitly directed to wound repair using a peptide inducer of syndecan expression which is effective only in particular cells [Column 1, lines 10-12; Column 2, lines 13-19]. The syndecans able to be induced in particular kinds of cells are syndecan-1 and syndecan-4 [Column 2, lines 27-30; Column 3, lines 16-18].

2. As disclosed by Gallo *et al.*, the composition of matter able to induce syndecan-1 and syndecan-4 expression in particular cells types is a 39 amino acid peptide termed "PR-39" and its biological active derivatives – all

of which (a) have the same or functionally equivalent structure, and (b) must include the amino acid sequences Pro-Pro-X-X-Pro-Pro-X-X-Pro and Pro-Pro-X-X-X-Pro-Pro-X-X-Pro, where X is any amino acid [Column 3, lines 26-34]. This syndecan-inducing composition of matter could also be part of a fusion protein, or be immobilized to an inert substrate, or be targeted using a specific ligand, or be a part of a longer protein [Column 3, lines 35-39].

3. The disclosed Gallo *et al.* composition of matter comprising the PR-39 required amino acid residue sequence are collectively identified as "syndecins". All such syndecins collectively must demonstrate specific biological activities which include: (a) the specific inducement of syndecan-1 and syndecan-4 expression on the surface of mesenchymal cells; (b) the specific inducement of syndecan-1 and syndecan-4 mRNA within mesenchymal cells; ©) an increase in the level of mesenchymal cell surface heparin sulfate; and (d) a rapid uptake into mesenchymal cells to a saturation level [Column 3, lines 39-46].

4. The PR-39 peptide composition as disclosed by Gallo *et al.* was identified, isolated from and found to be an active agent for inducing syndecan-1 expression as a component of wound fluid. Example 1 in the reference describes the experiment in detail [Column 6, lines 20-67; Column 7, lines 1-16]. Similarly, the degree of syndecan induction was

experimentally shown to vary directly with the concentration of PR-39 in wound fluid as described by Example 2 [Column 7, lines 20-67; Column 8, lines 1-23]. In this manner, the relationship between PR-39 in wound fluids and the induced expression of syndecan-1 and syndecan-4 in mesenchymal cells was empirically demonstrated and proven.

5. The selectivity of wound fluid and of PR-39 induction capability is then demonstrated within the '273 patent reference as being overtly controlled by particular cell type. As disclosed explicitly by Example 4 in the reference, all the non-mesenchymal cell types tested (4 major types) failed to respond to the effects of PR-39 in the wound fluid [Column 8, lines 51-65]. Only the mesenchymal cell varieties alone responded to the inducing effects of PR-39 in the wound fluid; and only the mesenchymal cell types alone showed the biochemical changes demonstrative of syndecan-1 induction [Column 8, lines 66-67; Column 9, lines 1-10].

6. As disclosed by the '273 patent, the explicitly stated uses and intended application for PR-39 peptide compositions is for wound repair via the induction of increased syndecan-1 and syndecan-4 mRNA levels [Column 2, lines 23-39]. Only in this manner will the PR-39 peptides function in promoting wound healing as well as treating other disorders involving mesenchymal cells and ligand interactions with cell surface heparan sulfate

[Column 2, lines 40-43]. These limited clinical applications and the explicitly stated demand and requirement which relies on the increased expression of syndecan-1 and syndecan-4 on the surface of mesenchymal cells using PR-39 peptides as the explicit means and manner by which the wound healing result is obtained – is set forth in detail within the text of the patent itself [Column 5, lines 1-67; Column 6, lines 1-17].

In sum, therefore, the following factual limits and requirements are explicitly taught by the disclosure of the Gallo et al. '273 patent reference:

(a) The PR-39 peptide is disclosed, empirically tested and presented as a peptide useful only for induction and expression of syndecan-1 and syndecan-4 on the surface of mesenchymal cells and is functional for the explicit purpose of increasing mesenchymal cell surface heparan sulfate.

(b) The PR-39 peptide is very selective as to particular cell type and is biochemically active as a "syndecin" only with cells of mesenchymal origin. The PR-39 peptide and its derivatives collectively are inactive with all cell types which are non-mesenchymal cells, especially cells of cerebral origin and epithelial origin.

©) The means and manner by which the PR-39 peptide exerts its biochemical effects is solely via the induction of cell surface syndecans and is limited to the consequential increase of cell surface heparan sulfate in cells of mesenchymal cell origin as the intended result.

(d) The explicitly stated value and intended function of the PR-39 peptides is as a healing agent for use with wounds and in clinical disorders which involve mesenchymal cells and ligand interactions with cell surface heparan sulfate. This explicitly stated mechanism of action and intended outcome is required in each and every clinical application disclosed without exception.

(e) Each of the PR-39 peptides must include the amino acid sequences Pro-Pro-X-X-Pro-Pro-X-X-Pro and Pro-Pro-X-X-X-Pro-Pro-X-X-Pro, where X is any amino acid. The is no exception to this explicit structural requirement and there are no PR-39 peptide compositions which are devoid of this amino acid residue sequence.

C. The Lack Of Relevance For The Gallo *et al.* Reference Of Record

1. As regards the factual basis presented by the Gallo et al '273 patent which the Examiners erroneously believe offers support for an anticipatory rejection, attention is directed to the written disclosure of the reference itself as exemplifying what the Examiner has employed wrongly and subjectively. These facts include the following points of information

(I) The PR-39 amino acid sequence must be employed as a 39 amino acid residue sequence at a minimum in order for biological activity to be demonstrated.

(ii) The entire 39 amino acid sequence of PR-39 might be part of a larger sized molecule such as a fusion protein, or when mobilized to an inert substrate or targeted using a specific ligand, as part of a longer length protein.

(iii) The entire PR-39 peptide (and any of its longer length products) are collectively identified as "synducins" – all of which require the ability to induce expression of syndecan-1 or syndecan-4 as the specific biological activity and mechanism of action described in the examples of the '273 patent.

(iv) The "synducin" characteristics and limited mechanism of action are solely for effecting the increased syndecan-1 and syndecan-4 expression on the surface of only mesenchymal cells; no type of cell other an a mesenchymal cell responds the effect of PR-39.

(v) The specific inducement of syndecan-1 and syndecan-4 mRNA within mesenchymal cells along is solely for purposes of causing an increase in the quantity of cell surface heparan sulfate.

(vi) The biochemically active PR-39 peptide compositions must include a specific and lengthy amino acid residue sequence which is Pro-Pro-X-X-Pro-Pro-X-X-Pro and Pro-Pro-X-X-X-Pro-Pro-X-X-Pro, where X is any amino acid.

2. The entire manner and means of use of the PR-39 peptide for any and all purposes is stated and explicitly limited within the '273 patent; and demands that the inducement of syndecans on the cell surface be a requisite outcome and consequence of the mechanism of action in each and every usage, clinically or otherwise. Thus, any composition or substance which employs and relies on the information disclosed by this '273 patent reference must follow and incorporate all the severe restrictions as stated explicitly by this reference in order for any utility or result to be expected or foreseen.

3. Equally important are the explicit limits of the method and compositions employed by this '273 patent. The use of the PR-39 peptides fails to be active with a variety of non-mesenchymal cells, as experimentally proven; and the '273 patent reveals that if the targeted cells are not mesenchymal cells as such, no functional response or biochemical activity will result or can be expected. In sum, all of the information disclosed or suggested by the '273 Gallo et al. patent is self-limiting and restrictive in its uses and applications.

4. With regard to the composition claims recited by presently pending claims 11and 12 (as well as by withdrawn claims 13 and 14), applicants note that this '273 patent reference teaches away from the

very characteristics, properties and utilities demonstrated by applicants' defined invention. Applicants note in particular that the peptide compositions defined by presently pending claims 11and 12 are all far shorter in length than the minimum 39 amino acid residue compositions demanded by the '273 patent; the claimed compositions are not a part of a fusion peptide or linked with any other molecule; and the claimed compositions do not comprise or contain the mandatory amino acid sequences which are explicitly required by the disclosure of the '273 patent reference. Thus, the Examiners have no basis at all within the '273 patent for either believing or suggesting that any shorter length peptide sequence – particularly those of 15 (or even of 11 or 8) amino acid residue length – could be or would be biologically active or functionally useful for any purpose.

Thus, for all reasons stated herein, applicants respectfully submit that multiple errors of fact and law have been made by the Examiners; and formally request that the Examiners reconsider their stated position and withdraw this ground of rejection against the presently pending claims. Applicants further submit and affirm that amended independent claims 11 and dependent claim 12 (as well as withdrawn claims 13 and 14 respectively) have patentable merit and are therefore allowable as presently worded.

In sum, applicants have addressed each basis of rejection stated in the instant Official Action forthrightly and objectively. In applicants' view, each issue or controversy has been evaluated, acted upon, and resolved completely. For these reasons, applicants respectfully submit and affirm that presently pending claims 11 and 12 (as well as withdrawn claims 13 and 14 respectively) are therefore now allowable.

In view of the above discussion and detailed review, applicants believe that this case is now in condition for allowance and reconsideration is respectfully requested. The Examiners are invited to call applicants' undersigned attorney should they feel that such a telephone call would further the prosecution of the present application.

Respectfully submitted,

MICHAEL SIMONS
YOUHE GAO

By: _____

David Prashker
Registration Number 29,693
Attorney for applicants
P.O. Box 5387
Magnolia, Massachusetts 01930
Tel: (978) 525-3794